

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

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in its capacity as elected Office

Date of mailing (day/month/year) 10 May 1999 (10.05.99)	
International application No. PCT/US98/19145	Applicant's or agent's file reference 33359-00/PCT
International filing date (day/month/year) 15 September 1998 (15.09.98)	Priority date (day/month/year) 19 September 1997 (19.09.97)
Applicant UDEM, Stephen, A. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
07 April 1999 (07.04.99)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

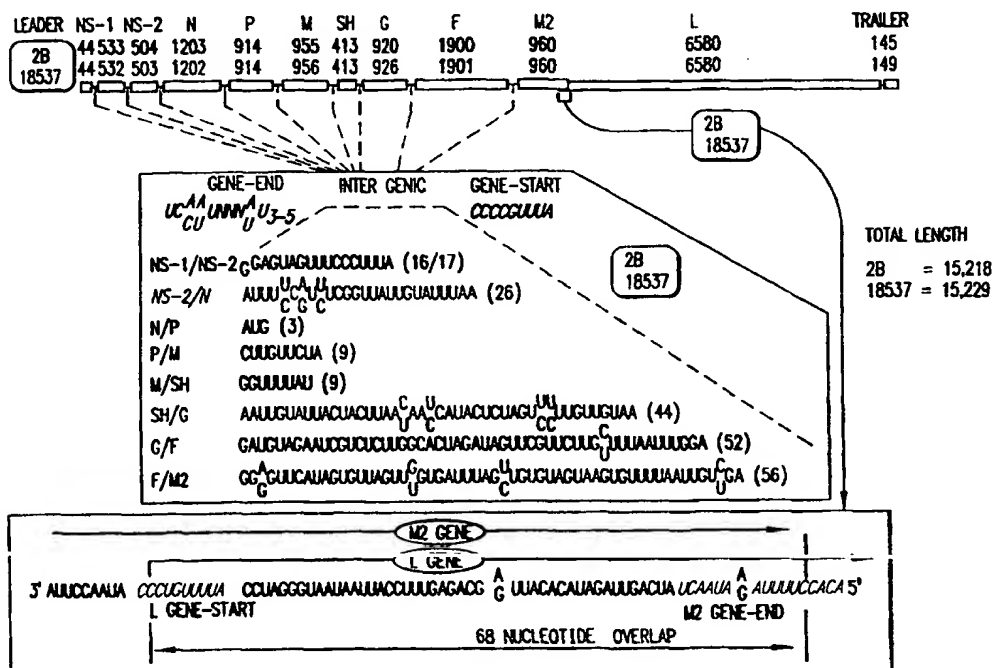
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Céline Faust Telephone No.: (41-22) 338.83.38
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p><b>(51) International Patent Classification <sup>6</sup> :</b>  <b>C12N 15/45, C07K 14/135, C12N 7/08, A61K 39/155</b></p>	<p><b>A1</b></p>	<p><b>(11) International Publication Number:</b>  <b>(43) International Publication Date:</b></p>	<p><b>WO 99/15672</b>  <b>1 April 1999 (01.04.99)</b></p>
<p><b>(21) International Application Number:</b> PCT/US98/19145</p> <p><b>(22) International Filing Date:</b> 15 September 1998 (15.09.98)</p> <p><b>(30) Priority Data:</b>  60/059,552                      19 September 1997 (19.09.97)      US</p> <p><b>(71) Applicant (for all designated States except US):</b> AMERICAN CYANAMID COMPANY [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).</p> <p><b>(72) Inventors; and</b></p> <p><b>(75) Inventors/Applicants (for US only):</b> UDEM, Stephen, A. [US/US]; Apartment 6F/G, 155 West 70th Street, New York, NY 10023 (US). SIDHU, Mohinderjit, S. [US/US]; 35 Lowell Drive, New City, NY 10956 (US). RANDOLPH, Valerie, B. [US/US]; 535 PineBrook Road, Lincoln Park, NJ 07035 (US).</p> <p><b>(74) Agents:</b> GORDON, Alan, M. et al.; American Home Products Corporation, Patent Law Dept. - 2B2, One Campus Drive, Parsippany, NJ 07054 (US).</p>		<p><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i></p>	

(54) Title: ATTENUATED RESPIRATORY SYNCYTIAL VIRUSES



**(57) Abstract**

Isolated, recombinantly-generated, attenuated, respiratory syncytial viruses of subgroup B having at least one attenuating mutation in the RNA polymerase gene are described. Vaccines are formulated comprising such viruses and a physiologically acceptable carrier. The vaccines are used for immunizing an individual to induce protection against respiratory syncytial virus.

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# INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 98/19145

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/45 C07K14/135 C12N7/08 A61K39/155

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, L	WO 98 13501 A (UEDEM S A ET AL.) 2 April 1998 (L: Priority) see page 62 - page 75; claims 12,13,22,23,38,39,45,46 ---	1-11
X	EP 0 567 100 A (AMERICAN CYANAMID COMPANY) 27 October 1993 see the whole document ---	1,3,5
P, X	WO 97 38138 A (UNIVERSITY OF MICHIGAN ;HERLOCHER M LOUISE; MAASSAB HUNEIN F) 16 October 1997 see claims 1-10 --- -/--	1,3,5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 January 1999

Date of mailing of the international search report

14/01/1999

Name and mailing address of the ISA

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Authorized officer

Cupido, M

# INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 98/19145

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 98 02530 A (US DEPARTMENT OF HEALTH;  WHITEHEAD STEPHEN S ; COLLINS PETER L;  JUHASZ) 22 January 1998  see claims 1,2,62</p> <p>-----</p>	1,3,5

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 19145

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 5 and 6  
are directed to a method of treatment of the human or animal  
body, the search has been carried out and based on the alleged  
effects of the vaccine.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/19145

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9813501 A	02-04-1998	AU 4427897 A	17-04-1998
EP 0567100 A	27-10-1993	AU 3705793 A	28-10-1993
		CA 2094464 A	22-10-1993
		JP 6022756 A	01-02-1994
		NZ 247444 A	22-12-1994
		ZA 9302763 A	08-02-1994
WO 9738138 A	16-10-1997	AU 2438597 A	29-10-1997
WO 9802530 A	22-01-1998	AU 3799797 A	09-02-1998

# PATENT COOPERATION TREATY

## PCT

REC'D 27 JAN 2000

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 33359-00/PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/19145	International filing date (day/month/year) 15/09/1998	Priority date (day/month/year) 19/09/1997
International Patent Classification (IPC) or national classification and IPC C12N15/45		
Applicant AMERICAN CYANAMID COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  07/04/1999	Date of completion of this report  24. 01. 00
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Nichogiannopoulou, A  Telephone No. +49 89 2399 8054  



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/19145

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-58 as originally filed

### Claims, No.:

1-11 as originally filed

### Drawings, sheets:

1/15-15/15 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/19145

been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**see separate sheet**

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims 7-10
	No:	Claims 1-6, 11
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-11
Industrial applicability (IA)	Yes:	Claims 1-4, 7-11
	No:	Claims 5, 6 see item V. 4.

### 2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US98/19145

**Re Item I**

**Basis of the report**

1. This opinion was established based on the application documents and the written sequence listing pages 1-85.

**Re Item II**

**Priority**

1. The following documents were published prior to the international filing date but later than the priority date claimed:

P1: WO 98 13501 A (UDEM S A ET AL.) 2 April 1998

P2: WO 97 38138 A (UNIVERSITY OF MICHIGAN) 16 October 1997

P3: WO 98 02530 A (US DEPARTMENT OF HEALTH) 22 January 1998

2. The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (19.09.1997). If it later turns out that this assumption is incorrect, P1-P3 will become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following document:

D1: EP-A-0 567 100 (AMERICAN CYANAMID COMPANY) 27 October 1993

2. The present application discloses the recombinant generation of an attenuated human RSV subgroup B, having an attenuating mutation in the RNA polymerase gene. The RSV 2B parental strain was attenuated by cold adaptation and screened for accumulation of temperature sensitive (ts) variants. The ts mutants were further screened and selected for vaccine candidates based on degree of attenuation and retention of neutralising epitopes. Amino acid changes in the polymerase protein L were identified that correlated with the desired phenotype.
3. **Novelty** (Article 33(2) PCT)  
Claims 1-6 and 11 are found to lack novelty and inventiveness for the following reason:  
Prior art document D1 discloses cold adapted mutant RSV, vaccine compositions containing such and methods of vaccination against RSV. The parental wild type strain RSV 2B was cold adapted and gave rise to mutant strains RSV 2Bp20L and RSV 2Bp33F. Nucleic acid molecules encoding cold-adapted mutant RSV are also provided. Although D1 does not explicitly disclose that strains 2Bp20L and 2Bp33F carry mutations in the polymerase protein L or the amino acid changes those mutations result into, these features are merely additional parameters of said strains, the disclosure of which cannot be used to restore their novelty. The parental RSV 2B strain as well as mutant RSV strains 2Bp20L and 2Bp33F have been deposited with the ATCC on March 19, 1992. Their sequences, as claimed in claim 11 have thus been generally available since that date.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US98/19145

**3. Inventive step (Article 33(3) PCT)**

Claims 7-10 are found to lack an inventive step under the terms of Article 33(3) PCT. The "rescue" system claimed has been applied to a variety of viruses (description page 20, line 35- page 21, line 8 and references therein) and thus belongs to the well established methodologies in the field. The application of such methodology for the production of the attenuated RSV of D1 is obvious to the skilled person and does not involve inventive activity.

**4. Industrial applicability (Article 33(4) PCT)**

Claims 5 and 6 -since they concern *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).